ABSTRACT

A significant amount of research has been devoted to studying phthalate-induced alterations in male reproductive development. In fact, studies in rodents have served to support the notion that a syndrome exists in the human male which captures phenotypic alterations such as hypospadias, cyptorchidism, poor semen quality, and even testicular cancer. Each phenotype in this 'testicular dysgenesis syndrome' is predicated on reduction in testosterone production by the fetal Leydig cell. We sought to examine the relationship between dysgenesis and steroidogenic capacity in the fetal rat testis more stringently by incorporating lower exposures than those typically used, conducting a comprehensive, non-targeted quantitative evaluation of the fetal testis proteome, and relating alterations in individual proteins to the capacity of the fetal Leydig cell to produce testosterone along with the histopathology of the fetal testis. For this, pregnant dams were dosed daily from gestation day (GD) 13-19 with 0, 10, or 100 mg diethyl hexylphthalate (DEHP)/kg body weight per orum. Each endpoint was represented by 16 litters (64 males). Testicular dysgenesis, specifically significant clustering of Leydig cells, occurred before any significant decrease in the capacity of the GD19 Leydig cell to produce testosterone when maximally stimulated with luteinizing hormone. At 100 mg DEHP/kg, testosterone production was reduced significantly, Leydig cell clusters became quite large, and additional dysgenetic changes were observed in the fetal testis. Of 23 proteins whose expression was altered significantly at both DEHP exposure levels, 7 were found to be correlated with and predictive of the various endpoints. None of these proteins have been previously implicated with DEHP exposure. Notably, pathway analysis revealed that these 7 proteins fit a pathway network in which each is regulated directly or indirectly by estradiol.